HERACLES: Hyperbolic Embeddings for Reconstruction and Analysis of Lineages

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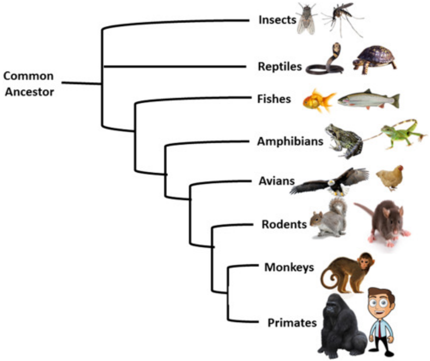
Outline

1. Background
2. Related Work
3. HERACLES Method
4. Conclusion

Background: Phylogeny

- **Phylogeny:** evolutionary development and diversification
- **Phylogenetic Tree:**

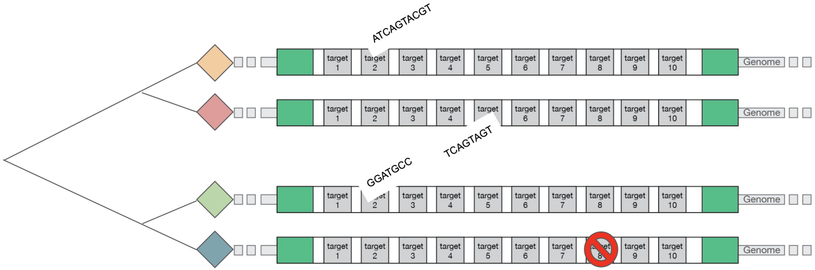


- **Idea:** Use inherited genetic alterations to infer phylogenetic trees

Background: CRISPR/Cas9

- Use CRISPR-Cas9 to precisely insert or delete genes in a cell at specific *target sites*
- These alterations will propogate through cell as they evolve
- In ”leaf cells”, examine the genes at target sites to reconstruct the cell lineage

Background: Character Matrix



Cells	Targets									
🔶	0	1	0	0	0	0	0	0	0	0
🟥	0	0	0	0	1	0	0	0	0	0
🟩	0	2	0	0	0	0	0	0	0	0
🔷	0	0	0	0	0	0	0	-	0	0

Figure from Anthony's presentation

Related Work: Methods for Lineage Tracing

Distance-Based Methods:

- Define pairwise distance function for two cells $d(c_1, c_2)$ that captures how ”far away” their sequences are
- Learn all-to-all distance matrix based D on d
- Construct tree from distance matrix D

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Maximum Likelihood:

- Assume statistical model of DNA sequence evolution
- Infer probability distribution for diffirerent configigurations of phylogenetic trees
- Optimize over continous branch lengths and *discrete* tree topologies

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Maximum Parsimony: identify phylogenetic tree with smallest number of evolutionary events to explain sequence data
Bayesian Inference: similar to maximum likelihood, but with Bayesian priors

Related Work: Wilson Paper

- **Paper:** *Learning Phylogenetic Trees as Hyperbolic Point Configurations* by Benjamin Wilson, 2021
- **Idea:** *Distance-based methods* in hyperbolic space can approximate *maximum likelihood methods*
- **Motivation:** Can embed a tree into hyperbolic space with an error bounded by 2δ

Theorem (Relaxed 4 Point Condition)

Let $\delta \geq 0$. A metric space (X, d) is said to be δ-hyperbolic if, for all $w, x, y, z \in X$,

$$d(x,w) + d(y,z) \leq \max\left\{d(x,y) + d(z,w),\ d(x,z) + d(y,w)\right\} + 2\delta$$

Related Work: Wilson Paper

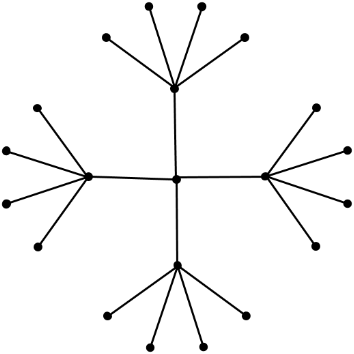

Figure: Euclidean Tree-Embedding

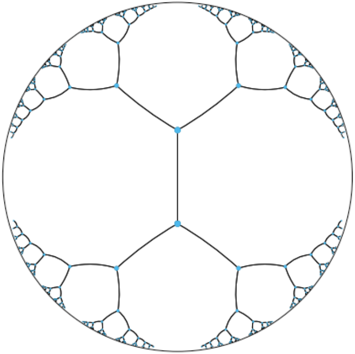

Figure: Hyperbolic Tree-Embedding

Related Work: Wilson Paper

For a Riemannian manifold $M = \mathbb{R}^m$, let a point configuration $\mathbf{x} = x_1 \dots x_n \in M$ with distance function d

For N cells and sequence data Θ of length L, let $\mathcal{L}_{ij}(t \mid \Theta)$ represent the likelihood of an evolutionary distance of t between cells i, j given sequence data Θ

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Our objective *logalike* function is

$$\mathbf{l}(\mathbf{x}) = \frac{1}{L} \sum_{i \neq j} \log \mathcal{L}_{ij}(d(x^i, x^j) \mid \Theta)$$

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Unlike typical log-likelihood on treespace, $\mathbf{l}(\mathbf{x})$ is on a Riemannian manifold and is differentiable in $\mathbf{x}$

Can compute $\nabla_{x^i} \mathbf{l}(x^i)$ to learn ideal point configuration for infering phylogenetic tree

Related Work: Wilson Paper

Let σ_i be the base/state at target site σ for cell i

Assume evolution is a continous time markov chain with transition probablities P, infinitesmial generator Q, and stationary distribution π.

Specifically let $P_{\sigma_i \sigma_j}(t)$ represent the probability of observing state σ_j t time steps after observing state σ_i under the Jukes-Cantor model of mutation:

$$P_{ab} = \begin{cases} \frac{1}{4} + \frac{3}{4} e^{-4t/3} := P_{\text{diag}} & \text{if } a = b \\ \frac{1}{4} - \frac{1}{4} e^{-4t/3} := P_{\backslash\text{diag}} & \text{otherwise} \end{cases}$$

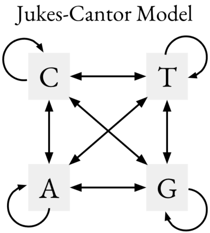

Figure from Sitara

Related Work: Wilson Paper

Objective logalike function:

$$\mathbf{l}(\mathbf{x}) = \frac{1}{L}\sum_{i\neq j} \log \mathcal{L}_{ij}(d(x^i, x^j) \mid \Theta)$$

Likelihood under assumed model of mutation

$$\mathcal{L}_{ij}(t) = \prod_{\text{sites } \sigma} \pi_{\sigma_i} P_{\sigma_i\sigma_j}(t)$$

$$\log \mathcal{L}_{ij}(t) = \sum_{\text{sites } \sigma} \log P_{\sigma_i\sigma_j}(t) + C$$

Expression for gradient with respect to cell *i*

$$\nabla_{x^i}\mathbf{l}(x^i) = \frac{1}{L}\sum_{\text{cells } j}\sum_{\text{sites } \sigma} \frac{(QP(d_{ij}))_{\sigma_i,\sigma_j}}{P(d_{ij})_{\sigma_i\sigma_j}} \nabla_{x^i} d_{x^j}$$

HERACLES Method: Model of Mutation

Accumulation of CRISPR-Cas9 mutations evolves as a continous time Markov Chain

Use a different model of mutation because known ancestral state, mutations cannot be undone, etc

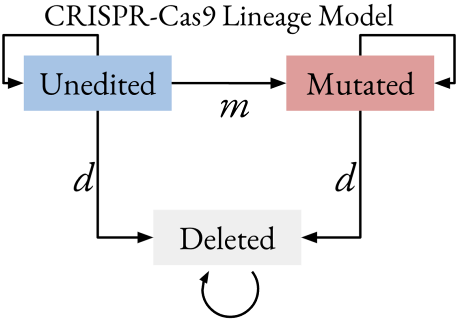

Figure from Sitara

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For a cell c at site σ, possible mutation states are unedited ϕ_c, mutations $1 \ldots M_\sigma$, or deleted D:

$$\sigma_c \in \{\phi_c, 1, 2 \ldots M_\sigma, D\}$$

For mutation states a, b, let $P^\sigma_{ab}(t)$ be the conditional probability of observing state b after t time units have passed since observing state a.

HERACLES Method

Because of time-irrervsersibility, distance betwen cells i, j at site σ is determined by distance from common ancestor to each cell.

Let $A(\sigma_i, \sigma_j)$ be the set of all possible ancestors of cells i, j at site σ. Let π_a be the prior of observing ancestral state $a \in A$

$$\mathcal{L}_{ij}(t) = \prod_{\text{sites } \sigma} \sum_{a \in A(\sigma_i, \sigma_j)} \pi_a \, P_{a\sigma_i}(\frac{t}{2}) \, P_{a\sigma_j}(\frac{t}{2})$$

Biological constraints ensure set of ancestral states is small

HERACLES Method

The infinitesmial generator Q is defined below

The time to leave the unedited state and transition to a mutated or deleted state follows an exponential distribution with rate $\gamma = \gamma_M + \gamma_D$

Given that a transition occurs to another character state, the transition to the observed character state C is $p_{\phi_\sigma, c}$

After transitioning to a character state, it may transition to a deleted state with rate λ_D

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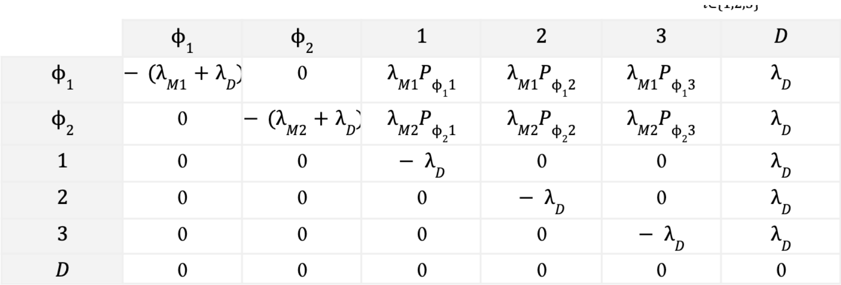
Infentiesmal generator Q is defined below with $\sum_i P_{\phi i} = 1$



$i\in\{1,2,3\}$

	ϕ_1	ϕ_2	1	2	3	D
ϕ_1	$-(\lambda_{M1} + \lambda_D)$	0	$\lambda_{M1}P_{\phi_1 1}$	$\lambda_{M1}P_{\phi_1 2}$	$\lambda_{M1}P_{\phi_1 3}$	λ_D
ϕ_2	0	$-(\lambda_{M2} + \lambda_D)$	$\lambda_{M2}P_{\phi_2 1}$	$\lambda_{M2}P_{\phi_2 2}$	$\lambda_{M2}P_{\phi_2 3}$	λ_D
1	0	0	$-\lambda_D$	0	0	λ_D
2	0	0	0	$-\lambda_D$	0	λ_D
3	0	0	0	0	$-\lambda_D$	λ_D
D	0	0	0	0	0	0

Probability transition matrix P is derived from Q:

$$P(t) = \mathrm{expm}(Q * t)$$

HERACLES Method

Objective logalike function:

$$\mathbf{l}(\mathbf{x}) = \frac{1}{L} \sum_{i \neq j} \log \mathcal{L}_{ij}(d(x^i, x^j) \mid \Theta)$$

Likelihood under assumed model of mutation

$$\mathcal{L}_{ij}(t) = \prod_{\text{sites } \sigma} \sum_{a \in A(\sigma_i, \sigma_j)} \pi_a \, P_{a\sigma_i}(\frac{t}{2}) \, P_{a\sigma_j}(\frac{t}{2})$$

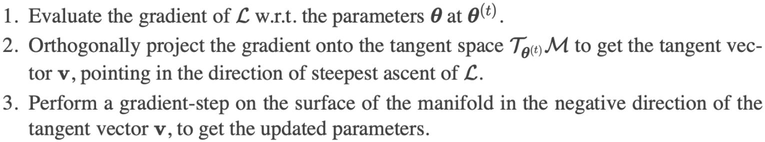
$$\log \mathcal{L}_{ij}(t) = \sum_{\text{sites } \sigma} \log \sum_{a \in A(\sigma_i, \sigma_j)} \pi_a \, P_{a\sigma_i}(\frac{t}{2}) \, P_{a\sigma_j}(\frac{t}{2})$$

Expression for gradient with respect to cell i

$$\nabla_{x^i} \mathbf{l}(x^i) = \frac{1}{L} \sum_{\text{cells } j} \sum_{\text{sites } \sigma} \frac{(QP(d_{ij}))_{\sigma_i, \sigma_j}}{P(d_{ij})_{\sigma_i \sigma_j}} \nabla_{x^i} d_{x^j}$$

HERACLES Method

Focused on implementing Riemannian SGD



1. Evaluate the gradient of $\mathcal{L}$ w.r.t. the parameters $\boldsymbol{\theta}$ at $\boldsymbol{\theta}^{(t)}$.
2. Orthogonally project the gradient onto the tangent space $\mathcal{T}_{\boldsymbol{\theta}^{(t)}}\mathcal{M}$ to get the tangent vector $\mathbf{v}$, pointing in the direction of steepest ascent of $\mathcal{L}$.
3. Perform a gradient-step on the surface of the manifold in the negative direction of the tangent vector $\mathbf{v}$, to get the updated parameters.

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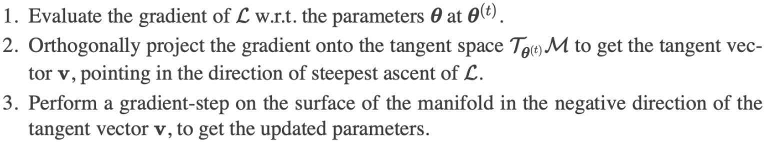

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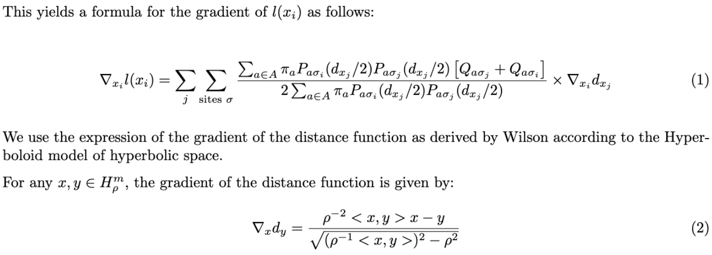
Already have gradient in closed form



This yields a formula for the gradient of $l(x_i)$ as follows:

$$\nabla_{x_i} l(x_i) = \sum_{j} \sum_{\text{sites } \sigma} \frac{\sum_{a \in A} \pi_a P_{a\sigma_i}(d_{x_j}/2) P_{a\sigma_j}(d_{x_j}/2) \left[Q_{a\sigma_j} + Q_{a\sigma_i}\right]}{2 \sum_{a \in A} \pi_a P_{a\sigma_i}(d_{x_j}/2) P_{a\sigma_j}(d_{x_j}/2)} \times \nabla_{x_i} d_{x_j} \tag{1}$$

We use the expression of the gradient of the distance function as derived by Wilson according to the Hyperboloid model of hyperbolic space.

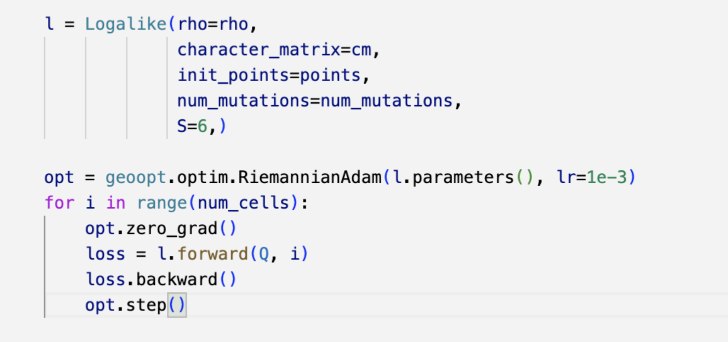
For any $x, y \in H^m_\rho$, the gradient of the distance function is given by:

$$\nabla_x d_y = \frac{\rho^{-2} < x, y > x - y}{\sqrt{(\rho^{-1} < x, y >)^2 - \rho^2}} \tag{2}$$

HERACLES Method

Use automatic differentiation to simplify implementation

Use geoopt package that extends PyTorch to work with Riemannian manifolds



```
l = Logalike(rho=rho,
             character_matrix=cm,
             init_points=points,
             num_mutations=num_mutations,
             S=6,)

opt = geoopt.optim.RiemannianAdam(l.parameters(), lr=1e-3)
for i in range(num_cells):
    opt.zero_grad()
    loss = l.forward(Q, i)
    loss.backward()
    opt.step()
```

HERACLES Method

Currently finishing implementation

- Compute prior ancestral states π_a
- Update simulated data with Caissopea package
- Extract rate variables for infentiesmal generator Q

Acknowledgements

Massive thank you to Sitara and Prof Pe’er for guidance.

(And thanks to Anthony for his prior work and walking me through his code)